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Barbara Fish and a Short History of the Neurodevelopmental Hypothesis of Schizophrenia

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The neurodevelopmental hypothesis of schizophrenia has become a paradigm broadly accepted in today's research in schizophrenia and its spectrum. This article traces the historical development of the neurodevelopmental hypothesis of schizophrenia up until the time of its explicit formulation in 1987, by Weinberger and by Murray and Lewis, with a main focus on the seminal contribution of Barbara Fish to its conception and elaboration.

Key words: schizophrenia/neurodevelopment/high risk studies/genetic risk/environmental risk/obstetric complications/pandysmaturation

Introduction

Thirty years ago, Weinberger[1,2] and Murray and Lewis[3,4] proposed, in separate publications, the neurodevelopmental hypothesis of schizophrenia. In essence, the hypothesis postulated that the combined effects of genes and an early brain lesion acquired during pregnancy or at birth increase the risk of schizophrenia. The lesion to fetal brain structures from early in life may remain latent until the critical periods of normal maturation and neuronal pruning, which "call" into operation the damaged structures, particularly the dorsolateral prefrontal cortex, resulting in prodromal and, subsequently, diagnostic symptoms of the disorder.

The aim of the current article is to trace the historical development of the neurodevelopmental hypothesis of schizophrenia up until the time of its explicit formulation in 1987, with a main focus on the seminal contribution of Barbara Fish to its conception and elaboration.

Background

Barbara Fish entered the scene of psychiatric research in the early 1950s as a child psychiatrist at the Cornell Medical Center in New York City. Her first article, "The detection of schizophrenia in infancy," was published in 1957,[5] at a time when psychoanalytic theory and practice reigned supreme in American psychiatry. According to medical historian Edward Shorter, "the influence of psychoanalysis reached into most of the private practices in the country. The biological psychiatrists, in contrast, had been limited to unglamorous posts in state hospitals."[6] In 1952, a joint report by the American Psychiatric Association and the Association of American Medical Colleges had proclaimed psychoanalytically oriented therapy for "the basic science of psychiatry." Influential clinicians, such as Harry Stack Sullivan, and anthropologists like Gregory Bateson, promoted the view of schizophrenia as a disorder of interpersonal communication within the family, where conflicting messages resulted in a confusing "double bind"[7] for the vulnerable child who failed to learn how to manage the concomitant anxiety and succumbed to psychosis. Other psychoanalysts proposed that the mother's coldness and unconscious rejection of the infant were the cause of later psychotic disorder. The related concept of the "schizophrenogenic mother," attributed to Fromm-Reichmann[8] and referring to a mix of overprotection and rejection, became a myth in the popular culture.[9]

Against this background, a "second biological psychiatry" (the first one being Adolf Meyer's eclectic "psychobiology") was gathering force.[6] Early genetic studies (Rosanoff et al[10] and Kallmann[11]) were based on samples of monozygotic and dizygotic twins and searched for Mendelian inheritance patterns by comparing concordant pairs (both twins affected) and discordant pairs (one twin affected) by schizophrenia. Barney Katz, a student of Rosanoff, compared the obstetric histories of 100 male schizophrenia patients and 100 healthy controls and

found a significantly higher incidence of obstetric trauma in the schizophrenia patients.[6] These studies were later succeeded by a methodologically much stronger research program initiated by Seymour Kety who, in 1959 started a study of children born to parent(s) diagnosed with schizophrenia but raised in foster homes, away from the primary family environment.[12] Much later on, in 1994, he and his Danish collaborators published the first results of the Danish Adoption Study.[13] In the Danish project, the prevalence of schizophrenia in the biological families of adoptees with schizophrenia was 10 times greater than in the biological relatives of the control adoptees. The findings clearly supported a genetic contribution to the transmission of the disorder and suggested that the mechanism of inheritance was polygenic.

Important concurrent development on the American scene was the arrival of psychopharmacology, with chlorpromazine as the first therapeutic agent, synthesized in France and introduced for clinical application in 1955 as a "neuroleptic" by Jean Delay and Pierre Deniker.[14] The psychopharmacological "revolution," which soon expanded to include antidepressant and anxiolytic drugs, stimulated new research into brain neurotransmitters, their biochemistry and receptors; cerebral neuroimmune mechanisms; and neuropathology in vivo, aided by the novel technologies of brain imaging. Classical brain histopathology, nearly forgotten during the "dynamic psychiatry" era, was revived and research into brain tissue samples from patients with schizophrenia was resumed. In one of those studies, Kovelman and Scheibel[15] described a widespread spatial disarray of the pyramidal neurons in the cortical layers that could only be explained by a failure of the migrating fetal neurons to reach their genetically predetermined targets. The authors concluded that this abnormality could not be a consequence of the disease but reflected a disruption of fetal brain development and represented a "neurohistological correlate of schizophrenia." Meanwhile, other insights were surfacing on the association between neurodevelopment and schizophrenia. Epidemiological studies (eg, James[16] and Pasamanick and Knobloch[17]) pointed at significant associations between a history of perinatal birth complications and emerging schizophrenia and other neuropsychiatric disorders. Bender and Helme[18] referred to maternal schizophrenia as a "diffuse encephalopathy" interfering with intrauterine brain maturation and manifesting with early speech impairment and "soft" neurological signs affecting the infant's motor coordination, gait, and muscle tone. Meehl[19] proposed the concept of *schizotaxia* as a genetically determined variant of personality development that may decompensate into psychosis under environmental stress. Against this background, the first Rochester International Conference on Schizophrenia took place in March 1967.[20] Prominent among the speakers were S. Kety, E.B. Brodie, T. Freeman, D. Rosenthal, T. Lidz, P. Venables, E. Kringlen, and S.A. Mednick. The major themes of the presentations included genetic, biochemical, and neuroscience topics, environmental and family studies and, notably, childhood schizophrenia. The general consensus reached at the Rochester conference was that schizophrenia is a multifaceted, likely heterogeneous entity that requires multidisciplinary approaches for its study.

Such was the intellectual environment which enabled Barbara Fish to embark on her ground-breaking longitudinal research into the fetal development and early predictors of schizophrenia risk.

The contribution of Barbara Fish

Exactly 60 years ago, in 1957, Fish published an article in the Journal of Nervous and Mental Disease, entitled "The Detection of Schizophrenia in Infancy," a title destined to arouse strong reactions ranging from hope to disbelief.[5] In that article, Fish reported in great detail the results of her "pilot" longitudinal study (begun in 1952–1953) of patterns of physical and mental health and development of 16 infants randomly chosen from a well-baby clinic in a socioeconomically deprived area in New York City. By 6 weeks of age, 25% of these infants were classified as "vulnerable to develop schizophrenia," based on abnormal development. By 3 years of age, these vulnerable subjects had developed clinical symptoms (anxiety, deviant body-image identification, problems in reality-orientation) whose frequency and severity closely fitted with each subject's degree of developmental immaturity at the beginning of the study. The most severely disturbed individual was "considered to be a schizophrenic child."[5]

No matter how brilliantly conducted, any study following 16 randomly chosen subjects to a maximum age of 3 years, in order to predict a disorder with a median onset age of 25–29 years and a lifetime population incidence of approximately 0.5–1% using criteria that had low credibility in the professional community, would face some hurdles. Well aware of this, Fish enlarged her sample's size, increased the sample's risk for schizophrenia by selecting babies born in a mental hospital to mothers with chronic schizophrenia, and extended the follow-up period. Results presented in 1975 were based on 24 individuals with longitudinal observations and independent follow-up data at 10 and 18 years of age.[21] Half of the subjects had mothers with chronic schizophrenia. By the 10 year follow-up, 2 of the 24 children had developed childhood schizophrenia while an additional 4 had non-psychotic disturbances (severe schizotypal personality disorders) belonging to the schizophrenia spectrum. Five of the 6 children had mothers with schizophrenia.

In choosing criteria predictive of future schizophrenia, Fish assumed that individuals not yet ill would have the same basic defects as individuals with manifest schizophrenia. Such characteristics had been previously identified by Fish's mentor, Bender,[22] in her 20 years of study of 850 children with a diagnosis of childhood schizophrenia.

The central problem underlying childhood schizophrenia was conceived to be early physiological immaturity, representing a lag in maturation at the fetal stage of development, occurring in all areas (motor, adaptive, language, personal-social), and leading to fundamental biological symptoms even in the absence of manifest schizophrenia. In Fish's own words, "The existence of identifiable physiological differences between the schizophrenic infant and the other infants at one month of age indicates that there is indeed *a biological predisposition*, and this was found to be *present before anxiety or personality symptoms as such were manifest*." And further, "The essence of the *biological disturbance* appeared to be in the *faulty timing and integration* of all aspects of development, including physical growth, *homeostatic* control, *neuromuscular* development and perceptual organization …. Further investigation into the underlying physiological disturbances in schizophrenic infants … should focus on the mechanisms which regulate the gradient, temporal pattern and total integration of development."[5](our emphases) This description of the neurodevelopmental model of schizophrenia was proposed 60 years ago.

Fish used paediatric, developmental, neurological and psychiatric exams to study her subjects, beginning at 4–6 weeks of age, and focusing especially on 6 characteristics that were central signs of the biological disturbance she was seeking: (a) homeostatic instability (eg, abnormalities of body thermogenesis, allergies, gastrointestinal problems), (b) fluctuation in consciousness (torporous states, disturbed sleep), (c) immature molluscous muscle tone, (d) infantile posture and motor activity, (e) overall plasticity, and (f) an unstable, uneven pattern of physical and mental development (eg, retardation and precocity in different areas at the same time, in the same area at different times, or even in the same area at the same time). The pattern characterizing schizophrenia was originally called *pandevelopmental retardation*[21] but later changed to *pandysmaturation* to encompass the instability and variation including precocious development—see criterion (f) above—that played a central role in differentiating schizophrenia-related abnormality from other neurological and intellectual disorders.

The Fish study had a tremendous effect on the genetic-based high-risk studies of schizophrenia initiated in the 1960s and 1970s,[23–25] as well as on a general orientation toward a neurodevelopmental theory of schizophrenia. At the same time, new studies capable of replicating Fish's spectacular results were few and far between, in no small part due to the difficulties involved. It would be 40–50 years before newer high-risk studies (with Fish's active participation) retested, confirmed, and extended her original findings. Studies in Israel[26] and Sweden[27] found that pandysmaturation was largely limited to offspring with parents with schizophrenia, predicted schizophrenia-spectrum disorder in the offspring in adulthood, and likely represented a genetic component of schizophrenia.

Sixty years ago, before the technological explosion including personal computing, whole genome scans and MRIs, Barbara Fish apparently "got it right the first time." One would guess she succeeded in doing so by maximizing the usefulness of the long clinical experience of her teacher, Lauretta Bender, by applying a dogged persistence in carrying out a difficult work-intensive study, using her extraordinary intelligence to dig her way through the massive data set and find the results, offering what were currently unpopular conclusions. However, she believed in her own results regardless of the a priori poor statistical chances of success. And possibly, as has been said in the world of ice hockey, "good goalies have a lot of luck."

The proliferation of studies of children at "high risk" for schizophrenia following Fish's publications

Growing interest in the relationship between neurodevelopment and schizophrenia, combined with an appreciable injection of research funding by the National Institute for Mental Health to build on that interest, led to much larger, longitudinal studies that adopted Fish's "high risk" approach, in following up children of parents with schizophrenia who were themselves at high risk of developing the illness. These studies used a battery of potentially predictive markers, including neurological, biological, behavioral, and cognitive variables to compare high-risk children with control children. The studies included, among others, the Copenhagen Project with its 2 waves of investigations in 1962 and 1972 which compared children of mothers with schizophrenia and matched control children without a family history of psychiatric hospitalisation[28,29]; the New York High Risk Project, started in 1971, comparing children of parents with schizophrenia with children whose parents had either an affective disorder or no history of mental illness[30]; the Jerusalem Infant Development Study, which included a replication analysis by Fish herself[26,31]; further studies in Sweden[32] and Helsinki[33]; and Rieder and Nichols's analyses utilising the National Collaborative Perinatal Project (NCPP) cohort born 1959–1966, comparing children of a parent with schizophrenia with matched controls and/or the full NCPP birth cohort[34]; some studies were able to control for environmental rearing effects by examining outcomes for children of parents with schizophrenia reared in adoptive or foster homes; these included an early US study from Oregon,[35] the Finnish Adoptive High Risk study,[36] and the Israeli High Risk study which also compared kibbutz-reared with home-reared high risk children.[37] A number of reviews describing the designs of these early studies and their findings corroborated and extended the earlier observations of Fish.[24,38–47]

The neurodevelopmental model of schizophrenia in the 1980s

As new tools for investigative medical research were developed and refined, findings from studies utilizing postmortem brains, neuroimaging, and other emerging technologies added fresh support to the observational data on disrupted neurodevelopment in schizophrenia. This included evidence of structural brain anomalies such as enlarged ventricles with decreased cerebral volume, morphological deviations that appeared to be nonprogressive, and an absence of cell gliosis or of other evidence of a degenerative brain disease.[48–50] Meanwhile, in 1982, Feinberg, building initially on evidence collected in his research on sleep, proposed a novel neurobiological model of disrupted neurodevelopment in schizophrenia that he had been refining over time.[51] This model, highly influential in its own right, postulated that schizophrenia was caused by errors in synaptic pruning in adolescence, although it was yet to be determined whether these abnormalities related to the elimination of too many, too few or the wrong synapses. Feinberg's observations added vital corroboration for schizophrenia as a neurodevelopmental disorder, albeit now positing a critical period of vulnerability in adolescence.

This burgeoning body of support for neurodevelopmental aberrations in schizophrenia led to models providing a robust etiological framework for understanding the disease. Already in 1981, Strauss and Carpenter[52] had outlined an interactive developmental concept of schizophrenia implicating genetic and gestational vulnerabilities, and the interplay between them. Meanwhile, a potential role for immune mechanisms interfering with fetal brain development was suggested by findings of associations with maternal exposure to influenza[53] and other viral infections,[54] albeit not consistently replicated.[55] By the late 1980s, this convergence of evidence was more formally articulated in independent publications by Weinberger[1,2] and Murray and Lewis[3,4] as a comprehensive neurodevelopmental hypothesis of schizophrenia. The model of neurodevelopment that they proposed was able to take account of the peculiarities of schizophrenia, including peak onset in late adolescence/early adulthood with a long delay between putative risk exposure and illness onset. In essence, these formulations of the neurodevelopmental model described a disruption of normal development of the central nervous system in utero or early infancy which manifested itself in adulthood as schizophrenia, but which also gave rise to deficits in psychophysiological and neurological functioning in childhood and early adolescence[3]—as earlier observed by Fish. Both sets of authors argued specifically for a subtle disease process or "brain lesion" that affected critical circuits in the brain in early development, with full-blown consequences evident many years later in adolescence or early adulthood as schizophrenia, when the affected brain areas reached physiological maturity. For Weinberger,[1,2] the original theory was open as to the etiology of the "lesion," whether it was genetically or environmentally determined, or both, with explicit reference to the potential impact of obstetric complications. The early articles by Murray and Lewis[3,4] were concerned primarily with obstetric complications as key environmental causes of the neurodevelopmental deviations observed, outlining the evidence and potential underlying mechanisms for their effects. Research into the role played by obstetric complications expanded in the years that followed, as access to and linkage across whole-population registers of midwives and psychiatric cases facilitated the growth of a new wave of risk factor epidemiological studies of schizophrenia, overcoming the limitations of clinical follow-up hampered by the long interval between risk exposure and disease outcome. Further refinements of the model gave scope for the integration of the early neurodevelopmental disruption observed by Fish and the later disruption described by Feinberg into 2- or even multi-hit versions of the model that accounted for the impact of varying permutations of genetic, obstetric, and other environmental insults along the developmental trajectory to schizophrenia.[56–58]

Conclusion: The Widening Horizon of Neurodevelopmental Research Today

Sixty years since Barbara Fish's seminal paper on the detection of schizophrenia in infancy, the neurodevelopmental model of schizophrenia has become a paradigm broadly accepted in today's schizophrenia research. Indeed, significant conceptual and methodological changes have occurred in the last decade: a tendency to view psychopathology as a continuum accessible through transdiagnostic studies; focus on first-episode psychotic disorders and early intervention; large-scale prospective cohort studies[59–65]; convergence between neurodevelopmental research and "big data" genetics; and genetically defined animal models. The neurodevelopmental theory of schizophrenia and its spectrum is being enriched by research into the maternal immune system, focusing on proinflammatory cytokines during pregnancy; neuronal migration abnormalities; excitotoxicity and oxidative stress—all of this leading toward a unified polygenic neurodevelopmental diathesis-stress model. We must pay homage to Barbara Fish for the fundamental stone she laid for the present edifice of burgeoning neurodevelopmental research.

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Conflict of Interest

None declared.

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